MAXIMIN CONTRAST FOR TESTING WHETHER MEAN RESPONSE INCREASES WITH DOSE LEVEL AT A CONSTANT RATE OR AT A DECREASING RATE: MAXIMIN SOLUTIONS FOR $k \leq 6$ EQUALLY SPACED DOSE LEVELS

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Abstract

The conventional method of partitioning the treatment sum of squares into single degree of freedom sums of squares utilizing orthogonal polynomials provides tests for curvilinearity. Such tests in practice are not usually based upon any firm belief that the response function is a polynomial, and a test such as "quadratic eliminating linear" is used operationally as a test for convexity or concavity. The power of this or any other orthogonal contrast among the deviations from linearity is an increasing function of the correlation between the contrast coefficients and the deviations of the true means from their regression on treatment levels. This correlation varies as the true (and unknown) means vary, and for any given contrast there is a convex (concave) configuration of the means which is least favorable for that contrast in the sense that correlation (and hence power) is minimized. The contrast having the largest minimum over the set of all possible convex configurations of treatment means is called the "maximin" contrast for testing convexity (or concavity). In the case of either $k=3$ or 4 equally spaced treatment levels this maximin contrast is the ordinary "quadratic eliminating linear" contrast. For $k=5$ the coefficients of the maximin contrast are $(-1,\ 2-\sqrt{1.75},\ 2\sqrt{1.75}-2,\ 2-\sqrt{1.75},\ -1)$ and the least favorable configurations of treatment means are the convex (or concave) segmented linear regressions with joins at the treatment levels.

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Introduction

A conventional procedure for testing linearity of a dose response curve is to fit a quadratic or higher degree polynomial curve to the data and test for improvement over the linear fit. Typically this is accomplished using orthogonal polynomials to partition the treatment (dose) sum of squares into single degree of freedom sums of squares due to "linear" regression, "quadratic eliminating linear", "cubic eliminating linear and quadratic", etc. Each of these contrasts is tested against an independent error mean square by an F-test, often overlooking the fact that a one-tailed t-test might be more appropriate; prior information frequently specifies, for example, that response cannot decrease with increasing dose (non-negative linear coefficient) or even more specifically that the rate of increase cannot be an increasing function of dose (non-positive quadratic coefficient).

Use of these orthogonal polynomial contrasts is not ordinarily based upon prior knowledge that the response curve is actually a polynomial; rather, the polynomial is used as a convenient approximation, and the test for "quadratic eliminating linear" is used operationally as a test for convex or concave curvature in the deviations from linear regression. We propose here to openly acknowledge this operational intent and provide an alternative contrast constructed to test more generally for convexity or concavity rather than to test specifically for quadratic curvature.

Maximin criterion

The statistical setting is taken to be a balanced one-way classification on dose levels; i.e., $Y_{ij} = \mu_i + \epsilon_{ij}$ for $i=1,\cdots,k$ and $j=1,\cdots,n$ with independent, normal and identically distributed errors. The linear dose response model H_{L+} specifies that μ_i is an increasing linear function of dose level X_i, $H_{L+}: \mu_i = \alpha + \beta X_i$, $\beta > 0$; i.e., prior knowledge is assumed to specify that response cannot decrease as the dose increases. If it is further known that the only alternative to an increasing linear response function is an increasing concave response function, then the alternative hypothesis becomes H_{M+C}: $\frac{(\mu_2-\mu_1)}{X_2-X_1} \geq \frac{(\mu_3-\mu_2)}{X_3-X_2} \geq \cdots \geq \frac{(\mu_k-\mu_{k-1})}{X_k-X_{k-1}}$ ≥ 0 with at least one strict inequality.

A contrast $\Sigma C_i \bar{Y}_i$, $\Sigma C_i = 0$, provides a one-tailed t-test of H_{L+},

$$T = \frac{\Sigma C_i \bar{Y}_i}{\sqrt{s^2 \Sigma C_i^2/n}}, \qquad s^2 = \frac{\Sigma\Sigma (Y_{ij} - \bar{Y}_i)^2}{k(n-1)}$$

if this test has size δ in H_{L+}; i.e., if $P_H(T>t) \leq \delta$ for all H in H_{L+}. This inequality imposes a constraint on $\underset{\sim}{C}$, for within H_{L+}

$$P_H\left\{\frac{\Sigma C_i \bar{Y}_i}{\sqrt{s^2\Sigma C_i^2/n}} > t\right\} = P_H\left\{\frac{\Sigma C_i(\alpha+\beta X_i + \bar{\epsilon}_i)}{\sqrt{s^2\Sigma C_i^2/n}} > t\right\}$$

$$= P_H\left\{\frac{\Sigma C_i \bar{\epsilon}_i}{\sqrt{s^2\Sigma C_i^2/n}} > t - \frac{\beta \Sigma C_i X_i}{\sqrt{s^2\Sigma C_i^2/n}}\right\}$$

and since $\beta > 0$ has no upper bound in H_{L+} than the size of the test can be less than unity only if $\Sigma C_i X_i \leq 0$. If the test is to be admissible the vector $\underset{\sim}{C}$ must in fact be orthogonal to $\underset{\sim}{X}$, for in H_{M+C} where $\mu_i \equiv \bar{\mu} + b_{\mu\cdot x}(X_i - \bar{X}) + e_{\mu_i\cdot x}$, $b_{\mu\cdot x} > 0$, the power of the test is

$$P_H\left\{\frac{\Sigma C_i \bar{\epsilon}_i}{\sqrt{s^2 \Sigma C_i^2/n}} > t - \frac{b_{\mu\cdot x} b_{c\cdot x} \Sigma(X_i - \bar{X})^2 + \Sigma C_i e_{\mu_i\cdot x}}{\sqrt{s^2 \Sigma C_i^2/n}}\right\} .$$

Since $b_{c\cdot x} \leq 0$ then

$$\frac{b_{\mu\cdot x} b_{c\cdot x} \Sigma(X_i - \bar{X})^2 + \Sigma C_i e_{\mu_i\cdot x}}{\sqrt{\Sigma C_i^2}} \leq \frac{\Sigma C_i e_{\mu_i\cdot x}}{\sqrt{\Sigma C_i^2}} \leq \frac{\Sigma e_{c_i\cdot x} e_{\mu_i\cdot x}}{\sqrt{\Sigma e^2_{c_i\cdot x}}}$$

with equality (for all $\underset{\sim}{\mu}$ in H_{M+C}) only if $b_{c\cdot x} = 0$; i.e., only if $C_i = e_{c_i\cdot x}$.

Power in H_{M+C} is thus expressible as

$$P_H\left(T > t\right) = P_H\left\{\frac{\Sigma e_{c_i\cdot x} e_{\bar{\epsilon}_i\cdot x}}{\sqrt{s^2 \Sigma e^2_{c_i\cdot x}/n}} > t - \frac{\Sigma e_{c_i\cdot x} e_{\mu_i\cdot x}}{\sqrt{s^2 \Sigma e^2_{c_i\cdot x}/n}}\right\}$$

$$= P_H\left\{\frac{\Sigma e_{c_i\cdot x} e_{\bar{\epsilon}_i\cdot x}}{\sqrt{s^2 \Sigma e^2_{c_i\cdot x}/n}} > t - r_{e_{c\cdot x} e_{\mu\cdot x}} \sqrt{\frac{\Sigma e^2_{\mu_i\cdot x}/\sigma^2}{s^2/(n\sigma^2)}}\right\}$$

and for a fixed value of the noncentrality parameter $\Sigma e^2_{\mu_i\cdot x}/\sigma^2$ the power is seen to be an increasing function of the correlation coefficient $r_{e_{\mu\cdot x} e_{c\cdot x}}$. For any given $\underset{\sim}{\mu}$ the choice of $\underset{\sim}{C}$ such that $e_{c\cdot x} = e_{\mu\cdot x}$ would make this correlation unity, so there is clearly no single contrast vector $\underset{\sim}{C}$ which uniformly maximizes $r_{e_{c\cdot x} e_{\mu\cdot x}}$ in H_{M+C}. A conservative choice can be made, however, by comparing contrasts on the basis of their minimum value of $r_{e_{c\cdot x} e_{\mu\cdot x}}$ in H_{M+C} and selecting one having the largest minimum. A contrast selected by this criterion is said to be <u>maximin</u> with respect to H_{M+C}.

Maximin solution when $X_i = i$; $i = 1, 2, \cdots, k \leq 6$

If the treatment design consists of k equally spaced dose levels then for $k = 3$ or 4 the maximin contrast for concavity may be easily shown to be the "quadratic eliminating linear" contrast, so we present here only the solution for the first nontrivial cases of $k = 5$ or 6 dose levels. The residuals $e_{\mu_i \cdot x}$ may be expressed as linear contrasts among increments $\mu_{i+1} - \mu_i$ with coefficients as shown in Table 1 for the case $k = 5$, and the sum of squares of residuals is expressible as a quadratic form in the differences among these increments; namely

Table 1. Deviations from the linear regression of treatment means μ_i on dose $X_i = i$, expressed as linear contrasts among the increments $\mu_{i+1} - \mu_i \geq \mu_i - \mu_{i-1} \geq 0$.

	$\mu_2 - \mu_1$	$\mu_3 - \mu_2$	$\mu_4 - \mu_3$	$\mu_5 - \mu_4$	H_{M+C} Sign of $e_{\mu_i \cdot x}$
$e_{\mu_1 \cdot x}$	-.4	0	.2	.2	-
$e_{\mu_2 \cdot x}$	.4	-.3	-.1	0	+
$e_{\mu_3 \cdot x}$	.2	.4	-.4	-.2	+
$e_{\mu_4 \cdot x}$	0	.1	.3	-.4	+
$e_{\mu_5 \cdot x}$	-.2	-.2	0	.4	-

$$\sum_{1}^{5} e^2_{\mu_i \cdot x} = .1\left[2\delta^2_{14} + 2\delta^2_{13} + 2\delta^2_{24} + \delta^2_{23}\right]$$

where $\delta_{ij} = (\mu_{i+1} - \mu_i) - (\mu_{j+1} - \mu_j)$. In H_{M+C} these differences are non-negative for $i < j$ and are partially ordered, and with no loss of generality we may take $\delta_{14} = 1$ so that

$$0 \le \delta_{23} \le \begin{Bmatrix} \delta_{13} \\ \delta_{24} \end{Bmatrix} \le \delta_{14} = 1 \quad .$$

A contrast $\underset{\sim}{C}$ which is orthogonal to dose levels satisfies two linear constraints which may be expressed as

$$C_3 = -3C_1 - 2C_2 + C_5 \qquad C_4 = 2C_1 + C_2 - 2C_5$$

and with no loss of generality we may take $C_1 = -1$ to agree with the sign of $e_{\mu_1 \cdot x}$ in $H_{\mu+c}$. The inner product with $e_{\mu \cdot x}$ then becomes

$$\sum_1^5 C_i e_{\mu_i \cdot x} = \delta_{13} + (1-C_2)\delta_{23} - C_5\delta_{34}$$

and

$$\sum_1^5 C_i^2 = 2(7+3C_2^2+3C_5^2-8C_2+7C_5-4C_2C_5) \;;$$

thus, $r_{e_{c \cdot x} e_{\mu \cdot x}}$ becomes

$$\frac{\delta_{13}+(1-C_2)\delta_{23}-C_5\delta_{34}}{\sqrt{.2(7+3C_2^2+3C_5^2-8C_2+7C_5-4C_2C_5)(2+2\delta_{13}^2+2\delta_{24}^2+\delta_{23}^2)}} \quad .$$

We first note that if, as in the cases $k=3$ and 4, the maximin contrast is symmetric with $C_i = C_{k-i+1}$ then $C_5 = C_1 = -1$ and

$$r_{e_{c \cdot x} e_{\mu \cdot x}} = \frac{1+\delta_{23}(1-C_2)}{\sqrt{.2(3C_2^2-4C_2+3)(2+2\delta_{13}^2+2\delta_{24}^2+\delta_{23}^2)}} \quad .$$

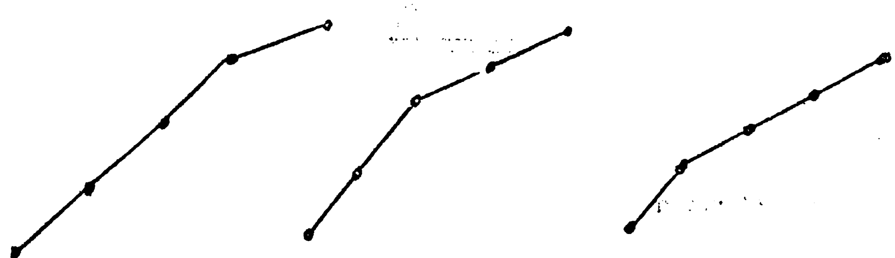
Since $\delta_{13} + \delta_{24} = \delta_{14} + \delta_{23} = 1 + \delta_{23}$ and $\delta_{23} \le \begin{pmatrix} \delta_{13} \\ \delta_{24} \end{pmatrix} \le 1$ then for fixed C_2 and δ_{23} the denominator is maximized when $\delta_{13}^2 + \delta_{24}^2 = 1 + \delta_{23}^2$; i.e., when either

$\delta_{13} = \delta_{14} = 1$ and $\delta_{24} = \delta_{23}$ or $\delta_{24} = \delta_{14} = 1$ and $\delta_{13} = \delta_{23}$; thus, for maximin purposes,

$$r = \frac{1+\delta(1-c)}{\sqrt{.2(3c^2-4c+3)(4+3\delta^2)}} \quad .$$

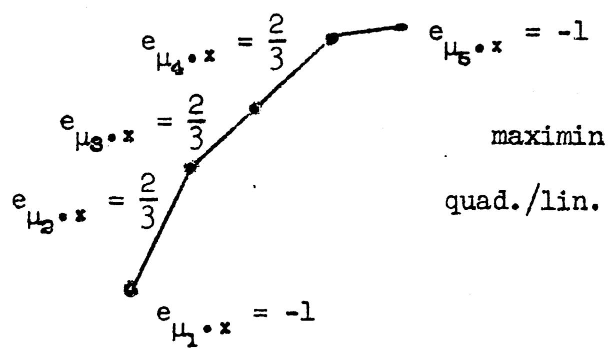
As a function of δ in $0 \leq \delta \leq 1$, this correlation strictly increases to a maximum at $\delta = 4(1-c)/3$ and then strictly decreases, provided that $\frac{1}{4} \leq c \leq 1$. The minimum value of r thus occurs at either $\delta = 0$ or $\delta = 1$, and the smaller of these two minima is as large as possible when the two are equal; i.e., when $1/\sqrt{4} = (2-c)/\sqrt{7}$, or $c = 2-\sqrt{7/4}$.

The maximin symmetric contrast $\underset{\sim}{c}$ is thus given by $\underset{\sim}{c}' = (-1,\ 2-\sqrt{7/4},\ 2(\sqrt{7/4}-1),\ 2-\sqrt{7/4},\ -1)$ or $\underset{\sim}{c}' \doteq (-1,\ .677,\ .646,\ .677,\ -1)$ in comparison with the "quadratic eliminating linear" $= (-1,\ .5,\ 1,\ .5,\ -1)$. The maximin value of r^2 is approximately .75 and is achieved at each of the three least favorable configurations illustrated below:



	$\delta_{13}=\delta_{14}$, $\delta_{24}=\delta_{23}=0$	$\delta_{13}=\delta_{23}=\delta_{24}=\delta_{14}$	$\delta_{14}=\delta_{24}$, $\delta_{13}=\delta_{23}=0$
maximin r^2	.75	.75	.75
quad./lin. r^2	.714	.918	.714

The slight increase in minimum power is achieved at very considerable expense in power loss at some interior points of H_{M+c}; the maximum r^2 achieved by the maximin contrast, however, is 1/1.0002 for μ-configurations of the form:



maximin $r^2 = \dfrac{1}{1.0002}$

quad./lin. $r^2 = .946$

For such a configuration the optimal contrast is (-1, 2/3, 2/3, 2/3, -1) which, for practical purposes, differs only negligibly from the symmetric maximin contrast and does have the property of being "somewhere most powerful".

Verification that the symmetric maximin contrast is, in fact, maximin may be obtained by noting that

$$\sum_1^5 c_i^2 = 2\left[3c_2^2-4c_2+3+3(c_5+1)^2+(1-4c_2)(c_5+1)\right]$$

and writing $r_{e_{c \cdot x} e_{\mu \cdot x}}$ as

$$r = \frac{1+(1-c_2)\delta_{23} - (1+c_5)\delta_{34}}{\sqrt{.1\Sigma c_i^2(2+2\delta_{13}^2+2\delta_{34}^2+\delta_{23}^2)}} \quad .$$

If $c_5 + 1 \leq 0$ then the least favorable configuration has $\delta_{34} = 0$, $\delta_{13} = \delta_{14} = 1$, $\delta_{24} = \delta_{23}$, giving

$$r = \frac{1+\delta_{23}(1-c_2)}{\sqrt{.1\Sigma c_i^2(4+3\delta_{23}^2)}}$$

and as a function of $c_5 \leq -1$, r is seen to be maximum at $c_5 = -1 = c_1$, which is the symmetric case already solved. A similar argument obtains if $c_5 + 1 \geq 0$.

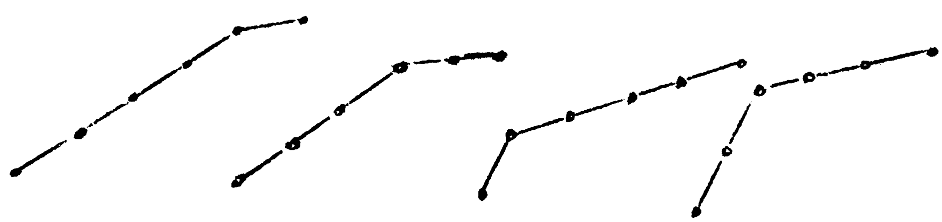
For k = 6 a similar argument gives

$$\underset{\sim}{c}' = (-1,\ 2-\sqrt{2.28},\ \sqrt{2.28}-1,\ \sqrt{2.28}-1,\ 2-\sqrt{2.28},\ -1)$$
$$\doteq (-1,\ .49,\ .51,\ .51,\ .49,\ -1)$$

in comparison to the "quadratic eliminating linear" contrast:

$$(-1,\ .2,\ .8,\ .8,\ .2,\ -1)\ .$$

The least favorable μ-configurations are the four convex segmented linear response functions with joins at the interior dose levels:



.7	.7	.7	.7	=	maximin r^2
.625	.888	.625	.888	=	quad./lin. r^2

In this case the maximin contrast is "most stringent, somewhere most powerful" since $\underset{\sim}{c}$ is concave. At the most favorable configuration, $\underset{\sim}{e}_{\mu\cdot x} = \underset{\sim}{c}$ and $r^2_{e_{c\cdot x}e_{\mu\cdot x}} = 1$, the quadratic/linear correlation is $r^2 = .906$; likewise, when the quadratic/linear correlation is unity then $r^2_{e_{c\cdot x}e_{\mu\cdot x}} = .906$.

The general form of the least favorable μ-configuration for testing concavity now seems apparent, consisting of all possible concave, two-phase linear segments joined at the interior dose levels, though no attempt has yet been made to verify either this or the conjectured symmetry of the maximin contrast. With unequal spacings the symmetry will certainly be lost and the effect upon the least favorable configurations is unknown. Presumably this same approach could be taken to construct a maximin test of sigmoidal shape (convex changing to concave), orthogonal to the contrast testing concavity, to replace the one degree of freedom test of "cubic eliminating linear and quadratic".